

09 /445154

UNITED STATES PATENT APPLICATION TRANSMITTAL FORM

BOX: PCT
ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231
Attention: DO/EO/US

430 Rec'd PCT/PIO 03 DEC 1999

Docket No.: 1348.017 USU

Sir:

Transmitted herewith for filing is the patent application of:

Applicant (s): Stephen Charles Williams, Bernadette Yon-Hin and Neil Blair
For: ELECTRODES FOR THE MEASUREMENT OF ANALYTES IN SMALL SAMPLE VOLUMES
International Application No.: PCT/GB98/01624
International Filing Date: June 3, 1998

ENTERING OF U.S. NATIONAL STAGE UNDER 35 U.S.C. §371

Transmitted herewith for filing are the following documents submitted under 37 C.F.R. §1.495(b) for the purpose of entering the national stage in the United States of America as an elected office.

Enclosed are:

- Unsigned Declaration/Power of Attorney;
- Sheet(s) of drawings (sheet);
- Specification, Claims and 1 sheet of Drawings as originally filed;
- Preliminary Amendment;
- An Assignment of the invention to: _____
including \$40.00 recordation fee, Check No.: _____
- Information Disclosure Statement with copies of document(s) and Form-PTO-1449;
- Signed verified Statement of Small Entity;
- Unsigned verified Statement of Small Entity;
- Priority of application Serial No. 9711395.5, filed on June 4, 1997 in Great Britain is claimed;
- Cover page of published PCT Publication No. WO 98/55856;
- Copy of International Preliminary Examination Report - PCT/IPEA/416 and 409;
- Copy of PCT/IB/308 - Communication of International Application to Designated Offices;
- Copy of International Search Report; and
- Copy of Request - PCT/RO/101.

09/445154

420 Rec'd PCT/PTO 03 DEC 1999

The Filing Fee is calculated below.

CLAIMS AS FILED				
(1) For	(2) Number Filed	(3) Number Extra	(4) Rate	(5) Basic Fee \$840
Total Claims	14 =	0	x \$18.00	\$0
Independent Claims	1 =	0	x \$78.00	\$0
Multiple Dependent Claim Fee			x \$260.00	= \$0.00
TOTAL FILING FEE				\$840.00
1/2 FILING FEE FOR SMALL ENTITY				\$420.00

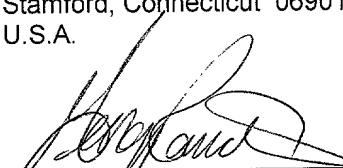
Check in the amount of \$420.00 to cover the filing fee (ck #519);

The Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. 1.16 and 1.17, which may be required with this communication or during the entire pendency of the application, or credit any overpayment, to **Deposit Account No. 01-0467**. A duplicate copy of this Form is enclosed.

Postcard.

Address all future communications to:

George W. Rauchfuss, Jr.
 Ohlant, Greeley, Ruggiero & Perle, L.L.P.
 One Landmark Square, Ninth Floor
 Stamford, Connecticut 06901
 U.S.A.



George W. Rauchfuss, Jr.
 Attorney for Applicant(s)
 Ohlant, Greeley, Ruggiero & Perle, L.L.P.
 Registration No. 24,459
 Telephone No. (203) 327-4500

December 3, 1999

Date of Signature

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Certificate No. EL522868560US, service under 37 C.F.R. §1.10 and is addressed to: Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231, Attention: DO/EO/US on December 3, 1999.

Lynn A. Maroldi

(Typed name of person mailing paper)



(Signature of person mailing paper)

USA

#3

Applicant or Patentee: Stephen Charles WILLIAMS et al Attorneys Docket No.

Application or Patent No: 09/445,154 Filed or Issued:

Title: ELECTRODES FOR THE MEASUREMENT OF ANALYTES IN SMALL SAMPLE VOLUMES

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS

(37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

the owner of the small business concern identified below:

an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN CAMBRIDGE SENSORS LIMITED

ADDRESS OF CONCERN Downhams House, Downhams Lane, Cambridge CB4 1XT
United Kingdom

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9 (d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in

the specification filed herewith.
 the application identified above.
 patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organisation having rights in the invention must file separate verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as small business concern under 37 CFR 1.9(d), or a non profit organisation under 37 CFR 1.9(e)

Each person, concern or organisation having any rights in the invention is listed below:

no such person, concern or organisation exists.
 each such person, concern or organisation is listed below.

Separate verified statements are required from each named person, concern or organisation having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28 (b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardise the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING

Mr. James McLarn.

TITLE OF PERSON OTHER THAN OWNER

Director.

ADDRESS OF PERSON SIGNING

1 church St, Fen Ditton, Cambridge

SIGNATURE

McLarn.

DATE Feb 28th 2000.

09 / 445154

420 Rec'd PCT/PTO 03 DEC 1999

Docket: 1348.017 USU

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Stephen Charles Williams et al.)

SERIAL No. To be allotted)
(based on PCT/GB98/01624 filed June 3, 1998))

FILED: Concurrently)

TITLE: ELECTRODES FOR THE MEASUREMENT OF)
ANALYTES IN SMALL SAMPLE VOLUMES)

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail in an envelope addressed to:

Box: P C T, Assistant Commissioner for Patents,
Washington, D.C. 20231, on December 3, 1999.

(Date of Deposit)

George W. Rauchfuss, Jr.

Name of Applicant, Assignee, or Registered Rep.


(Signature)

Box: P C T
Assistant Commissioner
for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Please amend this application as follows.

IN THE CLAIMS:

In Claim 1, line 16 thereof, please delete "on" and insert therefor ---at one edge of---

In Claim 3, line 1, please delete "or claim 2".

In each of Claims 4, 5 and 6, at line 1 thereof, please delete "any preceding claim" and insert therefor ---claim 1---.

In Claim 8, lines 3 and 4, please delete "any preceding claim" and insert therefor ---claim 1---.

Please add Claims 9 to 14 reading as follows.

Claim 9. A device according to claim 2, wherein the analyte is glucose and the reagent is glucose dehydrogenase.

Claim 10. A device according to claim 2, wherein the mesh is treated with a surfactant.

Claim 11. A device according to claim 2, wherein the mesh is additionally coated with a cell lytic agent.

Claim 12. A device according to claim 2, wherein the conductive layer comprises graphite particles, carbon particles and a polymer binder.

Claim 13. A device according to claim 12, wherein the graphite particles have an average size of 1-20 μm and a surface area of 1-50 m^2/g , and the carbon particles have an average size of 5-70 nm and a surface area of less than 150 m^2/g .

Claim 14. A method for the electrochemical analysis of an analyte in a liquid sample, which comprises applying the sample to the application area on a device according to claim 2, and quantifying the analyte by reaction with the reagent.

REMARKS

This Preliminary Amendment is presented to eliminate the improper multiple dependencies from the claims and to put Claim 1 in the form as shown on the amended

page 10 of specification attached to the International Preliminary Examination Report. The application is now ready for substantive examination on its merits.

Respectfully submitted,

By:



George W. Rauchfuss, Jr.
Reg. No. 24,459
Attorney for Applicant

Ohlandt, Greeley, Ruggiero & Perle, L.L.P.
One Landmark Square, Ninth Floor
Stamford, CT 06901-2682
Tel: (203) 327-4500
Fax: (203) 327-6401

Date: December 3, 1999

ELECTRODES FOR THE MEASUREMENT OF ANALYTES IN SMALL
SAMPLE VOLUMES

Field of the Invention

This invention relates to electrode devices which are capable of accepting small volumes of samples, and to their use in a test method for the detection and quantification of a test species present in a small sample volume.

Background of the Invention

Many devices have been disclosed, that are capable of accepting small volumes of sample material, and that allow analytes present in the sample to be interrogated, either by optical or electrical analytical processes. In particular, the use and construction of sample chambers capable of filling by capillary action has been described in both the patent and scientific literature. See, for example, EP-A-0170375 and US-A-5141868.

Such known devices may comprise electrodes deposited on a non-conducting substrate, coated with a reagent system specific for the analyte of interest and housed within a cavity whose dimensions are sufficiently small to allow introduction of a sample by capillary action. The sample is retained in close proximity to the electrodes, and the electrodes are configured in such a way as to facilitate the measurement of specific electrical properties of the sample.

Such devices suffer from numerous drawbacks, in particular the need to control the dimensions of the cavity within very tightly defined limits. Exceeding these manufacturing tolerances will prevent the sample from entering the cavity by capillary action.

Further, when viscous sample fluids such as blood are introduced into the cavity, the chamber will fill with sample relatively slowly, thus delaying the time taken to complete the analysis. Variations in sample viscosity and thus sample surface tension characteristics result in variations of the fill time; this not only compromises the overall analysis time but, more importantly, leads to

imprecision in the analytical result, since the time over which the sample is exposed to the analyte-specific reagent is subject to variation.

WO-A-9730344 discloses an electrode device which includes a polyester mesh adapted to guide the sample to the reference electrode. This device requires that the reagent includes a filler having both hydrophobic and hydrophilic surface regions, in order to avoid problems associated with variations in sample handling and to be independent of the haemocrit of the sample, for glucose testing.

According to the Invention

According to the present invention, a device which is capable of electrochemical measurement of the levels of analytes present in a small fluid sample volume, comprises a conductive layer coated with an analyte-specific reagent and deposited on a non-conducting substrate, a spacer layer deposited onto the non-conducting substrate by thick film printing, a monofilament mesh material coated with a surfactant and/or a chaotropic reagent, the mesh being overlaid onto the space layer, and a second non-conductive substrate adhered to the mesh layer. The device is thus multilayer in construction, and comprises two surfaces separated by a printed spacer layer and forming a cavity or area which is open at one end for the introduction of sample. This cavity or area is filled with a mesh material that extends beyond the second substrate and forms a sample application area.

A device according to the present invention may be produced and used by the steps of

(a) depositing a conducting layer of carbon and graphite, in a polymer binder, on a first non-conducting substrate;

(b) depositing a second conducting layer consisting of silver/silver chloride to function as a reference/counter electrode, adjacent to but not continuous with the first conducting layer;

(c) coating the surface of the first conductive layer with a reagent or mixtures of reagents which react specifically with an analyte or analytes in a sample material;

5 (d) forming a spacer layer by thick film printing on top of the first non-conducting substrate and on top of the first conducting layer, in order to leave a portion of each of the first and second conducting layers exposed;

10 (e) locating a coated mesh material on top of the spacer layer and permanently securing it to the spacer layer;

15 (f) locating a second non-conducting substrate on top of the mesh material and permanently securing it in such a way as to leave an extended area of mesh exposed;

(g) applying a sample to the extended mesh area in order to fill or flood the device sensing area, by wetting of the mesh with sample; and

20 (h) quantifying the analyte in the sample by reaction with the reagent on the first conducting layer.

The electrode device allows the application of a small volume of sample (typically less than 2 μ L) to the mesh extension. This is followed by flooding of the device sensing area with sample, bringing it into intimate contact with the measuring electrodes. The cavity may be filled 25 either by placing a drop of sample liquid on top of the exposed mesh at the edge of the cavity or by contacting the edge of the cavity with the sample.

Description of the Invention

30 The accompanying drawings are provided for the purpose of illustration only. In the drawings:

Fig. 1A is a schematic side view of a sensor device embodying the present invention; and

Fig. 1B is a plan view of part of the embodiment shown in Fig. 1A.

35 In more detail, the drawings show a non-conducting sheet 1 and, deposited thereon, a conducting electrode in two parts 2a,2b. The part 2a carries a reference/counter

electrode 3, and the part 2b carries a reagent layer 5. The parts 2a, 2b also carry a spacer layer 4 (this and other components described below are not shown in Fig. 1B, which is provided merely to show the electrical configuration). A mesh material 6 is laid over the electrode 3, the spacer 4 and the reagent layer 5. A tape 7 is provided over the mesh material 6.

A device sensing area 8 is defined between the respective parts of the conductive layer and thus between the reagent and the reference electrode. The mesh material is not coextensive with the tape 7, thereby defining a sample application area 9. In use, sample applied to area 9 is carried by the mesh 6, so that it floods areas 3, 5 and 8. The presence of an analyte in the sample can now be determined electrochemically.

Description of the Invention

The mesh material is interposed between the spacer layer (on the first substrate) and the second substrate, and functions to reduce the surface tension and/or viscosity of the sample, by virtue of the wetting agent coated onto its surface. Application of sample to the extended portion of the mesh, results in dissolution of the mesh coating material into the sample, reducing sample surface tension and allowing sample to flow into the device cavity. Sample will not enter the device cavity in the absence of a wetting reagent coated onto the mesh. Alternatively, in complex samples such as blood, where the measurement of a specific analyte is adversely affected by the presence of whole cells, for example by poisoning an electrode surface, the mesh may be coated with an agent which lyses the cells on contact; this has the added advantage of reducing sample viscosity at the same time, whilst removing the whole cell interference.

The system may be deposited as a single electrode, a micro-electrode or as a microelectrode array. The electrode may be used in conjunction with reference/counter electrodes deposited on the same substrate.

The non-conducting substrate material may be a sheet of, for example, polyester, polycarbonate, polyvinyl chloride, high density polypropylene or low density polypropylene. In a preferred embodiment, a polyester sheet material is heat-stabilised prior to application of the conducting layers, to confer dimensional stability on the polyester material prior to processing.

The conducting layer preferably contains graphite, carbon and a polymer binder. For example, the graphite component has an average particle size of up to 20 μm , e.g. 1-20 μm , a typical surface area of up 50 m^2/g , e.g. 1-50 m^2/g . It is inherently conductive; it may be derived from either natural sources or produced synthetically. The carbon component preferably has an average particle size less than 1 μm , e.g. 5-70 nm, and a typical surface area of less than 150 m^2/g . Like the graphite component, it is also inherently conductive.

The polymer binder may be either thermoset or thermoplastic. It may be derived from any of diverse polymer families, including vinyl chloride, vinyl acetate, vinyl alcohol (and copolymers of vinyl chloride, acetate and alcohol), hydrocarbons, ethyl and methyl celluloses, epoxys, polyesters, alkyds and polymers containing functional reactive groups such as carboxyl, hydroxyl, amine, thiol, ester, epoxide and amide groups, which enable the polymer to be cross-linked.

The conducting electrode material may be deposited on the non-conducting substrate by a conventional printing process, e.g. thick film printing (also known as screen printing), lithography, letterpress printing, vapour deposition, spray coating, ink jet printing, laser jet printing, roller coating or vacuum deposition. Following deposition of the conductive electrode material, the polymer binder may be stabilised or cured by a number of conventional processes, including forced air drying, forced air drying at elevated temperatures, infra-red irradiation, ultraviolet irradiation, ion beam irradiation or gamma

irradiation. All of these processes result to varying degrees in the cross-linking of individual molecules of the polymer binder. The use of ultraviolet radiation requires the inclusion of a photo-sensitising reagent in the 5 conductive electrode material, to initiate the polymer cross-linking reaction.

The reagent located on top of the first conductive layer is characterised in that it contains all the components in a solid state necessary for measuring the 10 concentration of analyte in a sample. Such components include enzymes, enzyme cofactors, coenzymes, co-substrates, antibodies or other analyte-binding partners, DNA or RNA, redox partners, buffers, ionophores and salts.

15 The reagent may also support matrices, binders and stabilisers for the other components. For example, suitable matrices include particles of graphite, carbon, silica, glass, latex or polyvinyl chloride. Suitable binders include polyvinyl alcohol, polyvinyl acetate, 20 polyvinyl pyrrolidine, proteins, cellulose and cellulose acetate. Suitable stabilisers include alcohols, esters, proteins, protein hydrolysates and both simple and complex carbohydrates.

25 The reagent may comprise a number of individually applied layers, each containing specific components. Its composition is such that it undergoes at least partial dissolution when contacted by the fluid sample.

30 The reagent may be deposited on the first conducting layer by a conventional deposition process, e.g. thick film printing (also known as screen printing), lithography, letter press printing, vapour deposition, spray coating, ink jet printing, laser jet printing, roller coating or vacuum deposition. Combinations of these deposition processes may be used to construct a multilayer. Following 35 deposition of the reagent (or after deposition of each individual layer), the layer may be stabilised or cured by a number of conventional processes, including those

described above, in order to achieve cross-linking of individual molecules of the polymer binder.

The spacer layer may be deposited on the first non-conducting substrate by conventional thick film deposition, and may be stabilised or cured by a number of conventional processes, including those described above, in order to cross-link individual molecules of the polymer binder. The thickness of the spacer layer may be controlled by means of a number of parameters, including printing conditions (pressure, speed, screen tension and emulsion thickness) and ink properties such as solids content and viscosity.

The mesh layer is preferably a synthetic, monofilament, woven material. It may be made from polyester or nylon. The mesh is coated with a surfactant material, a detergent or wetting or lysing agent. Examples include fluorosurfactants, non-ionic surfactants, ionic surfactants, zwitterionic surfactants, saponin and sodium cholate.

Electrodes of the invention have several desirable characteristics. For example, the devices require a very small volume, typically less than 2 μL , of sample such as whole blood, plasma, serum, interstitial fluid, sweat or saliva. When the sample fills the sample cavity, a very thin film of sample is spread across the surface of the deposited reagent, maximising contact with the reagent, and enabling reagent to be dissolved in the sample rapidly. This allows rapid attainment of the steady state.

In a preferred embodiment of the device, the cavity is positioned at the end of edge of the device. This device may be readily filled with sample by contacting the edge of the test strip with the sample. In another preferred embodiment, the cavity may be positioned 0-2 mm from the edge of the device, thus exposing an area of the test strip which may be scraped along a surface (such as a punctured area of skin), in order to collect the sample.

Electrodes of the invention may be used for the analysis of analytes/species which can be directly oxidised or reduced by the removal or addition of electrons at an electrode; analytes/species which can be readily converted, 5 by an enzyme or a series of enzymes, to a product which can be directly oxidised or reduced by the removal or addition of electrons at an electrode; analytes/species which can be converted to a product by an enzyme, with the concomitant oxidation or reduction of an enzyme cofactor, wherein the 10 cofactor may then be directly oxidised or reduced by the addition/removal of electrons; and analytes/species which can be converted to a product by an enzyme which is in intimate contact with the electrode surface, such that the enzyme is able to pass or receive electrons directly from 15 the electrode. The novel device is particularly suitable for use as a glucose sensor. In this case, the reagent is preferably glucose dehydrogenase; this can provide a glucose reading that is substantially independent of the haemocrit of the sample.

20 The following Example illustrates the invention.

Example

A conductive ink material is printed onto a non-conducting polyester sheet material (125 μm thick) by a screen printing process. The conductive ink material 25 consists of a mixture of graphite particles (average particle size 1 μm , with a surface area of 15 m^2/g), conductive carbon particles (average particle size 40 nm, surface area 100 m^2/g), and a vinyl chloride/acetate copolymer binder in an organic solvent. After deposition 30 of the conductive ink, solvents are removed in a forced air oven, whilst the application of elevated temperature initiates the chemical cross-linking of polymer binder by the bifunctional amine.

A silver/silver chloride, screen-printed 35 reference/counter electrode is located adjacent to the conductive carbon layer on the polyester support. A spacer layer is then screen-printed in such a way as to leave part

of the conductive carbon electrode and all of the reference/counter electrode exposed.

A multilayer reagent mixture, specific for the measurement of glucose, is prepared. It comprises 2,6-dichlorophenolindophenol, Nile Blue, Medola Blue or any other suitable mediator for the enzyme cofactor NADH, deposited onto the exposed conductive carbon/graphite layer from aqueous solution by pipetting, and dried to leave a film of mediator coated onto the conductive carbon/graphite layer. A second layer is deposited by thick film printing, consisting of a mixture of graphite, NAD^+ , buffer salts, surfactants, stabilisers and rheology modifiers. This is then dried. A third layer is deposited by pipetting, consisting of an aqueous solution of glucose dehydrogenase (NAD-dependent), buffer salts and stabilisers. That is then also dried.

A surfactant-coated monofilament mesh material is located on top of the spacer layer and secured by thick film deposition of a second spacer layer. A second non-conducting layer, comprising a 75 μm thick polyester tape material coated on one side with a pressure-sensitive adhesive, is positioned on top of the monofilament mesh in such a way as to leave an extended area of the mesh exposed. The exposed area acts as a sample application zone.

When a suitable potential difference is applied between the conductive carbon and the silver chloride reference electrodes, the electrode device can be used for the measurement of glucose in a sample of blood, using standard electrochemical techniques such as chronoamperometry. Glucose is converted to gluconolactone, with concomitant conversion of NAD^+ to NADH by the action of the NAD^+ -dependent glucose dehydrogenase, and NADH is reoxidised to NAD^+ by the mediator compound. The mediator compound is in turn reoxidised at the electrode surface, and the current produced is proportional to the concentration of glucose in the sample.

M 14.05.98

10

CLAIMS

1. A device for use in the electrochemical analysis of an analyte in a liquid sample, which comprises:
 - a non-conducting substrate;
 - 5 a conductive layer, deposited on the substrate, in two parts, defining a non-conducting gap therebetween;
 - an analyte-specific reagent coated on the conductive layer, on one side of the gap;
 - 10 a reference electrode on the conductive layer, on the other side of the gap;
 - a spacer layer deposited over the conductive layer;
 - a monofilament mesh coated with a surfactant or chaotropic agent, the mesh being laid over the reagent, the reference electrode and the spacer layer; and
 - 15 a second non-conductive layer, adhered to the mesh layer, but not coextensive therewith, thereby providing a sample application area at one edge of the mesh.
2. A device according to claim 1, wherein the reagent is free of filler having both hydrophobic and hydrophilic surface regions.
3. A device according to claim 1 or claim 2, wherein the analyte is glucose and the reagent is glucose dehydrogenase.
4. A device according to any preceding claim, wherein the mesh is treated with a surfactant.
- 25 5. A device according to any preceding claim, wherein the mesh is additionally coated with a cell lytic agent.
6. A device according to any preceding claim, wherein the conductive layer comprises graphite particles, carbon particles and a polymer binder.
- 30 7. A device according to claim 6, wherein the graphite particles have an average size of 1-20 μm and a surface area of 1-50 m^2/g , and the carbon particles have an average size of 5-70 nm and a surface area of less than 150 m^2/g .

8. A method for the electrochemical analysis of an analyte in a liquid sample, which comprises applying the sample to the application area on a device according to any preceding claim, and quantifying the analyte by reaction
5 with the reagent.

09/445154

WO 98/55856

PCT/GB98/01624

1/1

Fig. 1A.

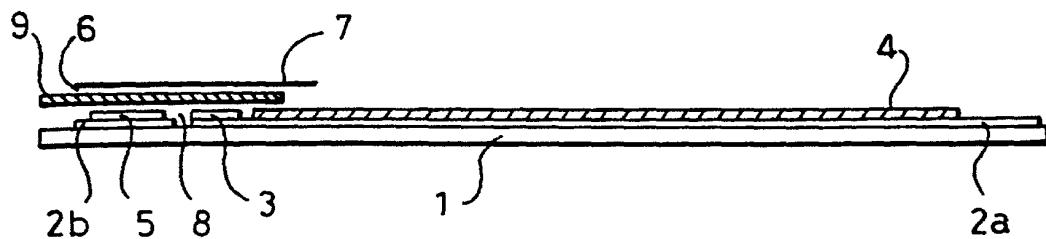
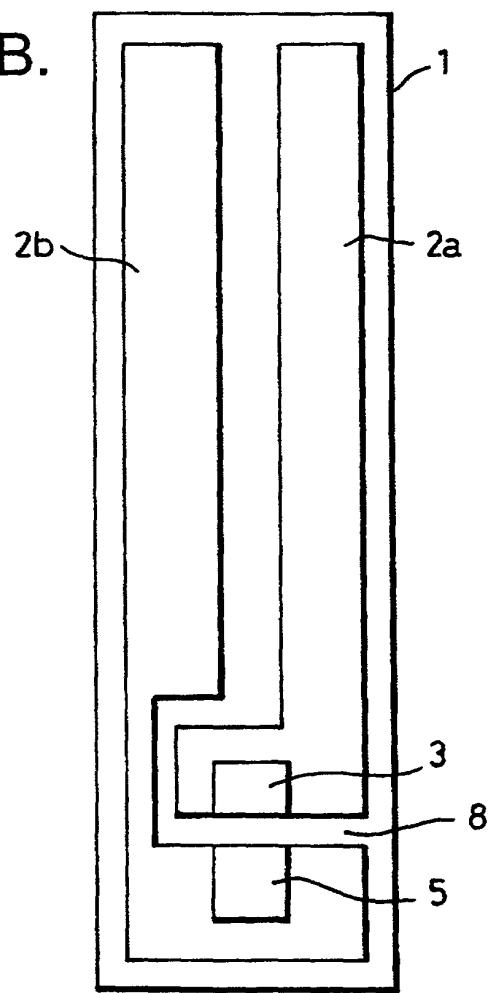


Fig. 1B.



DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled
ELECTRODES FOR THE MEASUREMENT OF ANALYTES IN SMALL SAMPLE VOLUMES

the specification of which is attached hereto or

was filed on 03 JUN 1998 as United States Application Number or PCT International Application Number PCT/GB98/01624 and was amended on 12 MAY 1999 (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for a patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached?
			<input type="checkbox"/>	YES <input type="checkbox"/> NO <input type="checkbox"/>
9711395.5	GB	04 JUN 1997	<input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:
John F. Ohlandt, Reg. No. 19,615; Paul D. Greeley, Reg No. 31,019; Charles N. J. Ruggiero, Reg No. 28,468; David N. Koffsky, Reg No. 19,905; George W. Rauchfuss, Jr., Reg No. 24,459 and Dallett Hoopes, Reg No. 18,846

Direct all correspondence to:

Ohlandt, Greely, Ruggiero & Perle
One Landmark Square, Suite 903
Stamford, CT 06901
USA



I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

1-00
Full name of sole or
First Inventor Stephen Charles WILLIAMS

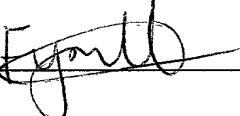
Inventor's signature 

Residence address California, USA

Post Office address P O Box 3559, 500 Stone Pine Road Half Moon Bay, CA
94019, USA

Country of Citizenship United Kingdom Date of signature 23 January 2002

2-00
Full name of
Second Inventor Bernadette YON-HIN

Inventor's signature 

Residence address Cambridge, United Kingdom

GBN

Post Office address c/o Cambridge Sensors Limited, Downhams House
Downhams Lane, Cambridge CB4 1XT, United Kingdom

Country of Citizenship United Kingdom Date of signature 4 November 99

3-00
Full name of
Third Inventor Neil BLAIR

Inventor's signature 

Residence address Cambridge, United Kingdom

GBN

Post Office address 122 Limes Road, Hardwick, Cambridge CB3 7XU
United Kingdom

Country of Citizenship United Kingdom Date of signature 5 November 1999